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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,573	03/22/2004	Anat Blumenfeld	13572-105040US5	2196

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/806,573	BLUMENFELD ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed October 10, 2007. Applicants' amendments and arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Election/Restrictions

2. This application contains claims 18 and 19 drawn to an invention nonelected with traverse in the reply filed on November 15, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Maintained Rejections

Claim Rejections - 35 USC § 112 second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is indefinite over the recitation of "corresponding polymorphism pattern." Corresponding is not an art recognized term to describe the relationship between two nucleic acid sequences or two polymorphism patterns. It is not clear as to whether a corresponding polymorphism or polymorphism pattern refers to

polymorphisms of the same identity and at the same nucleotide location within the genome or to polymorphisms of similar identity or at similar locations within the genome (e.g., polymorphisms linked to another polymorphism or located near the polymorphism). Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates " to nucleic acid sequences, one of skill in the art cannot determine what would constitute a corresponding polymorphism pattern and thereby cannot determine the meets and bounds of the claimed subject matter.

Response to remarks:

In the response, Applicants state that the claims have been amended to remove the term "corresponding." However, claim 28 has not been amended to delete this term or to otherwise address the above rejection.

Claim Rejections - 35 USC § 112 – Written Description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-28 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 20-28 and 30-33 are drawn to a method for detecting the presence of a polymorphism linked to a gene associated with familial dysautonomia (FD) comprising analyzing a region of chromosome 9 for a polymorphism located between D9S59 and D9S127 inclusive wherein the presence of the polymorphism is indicative of carriers of a gene associated with familial dysautonomia. The claims do not define the structure of any polymorphisms located between D9S59 to D9S127 (i.e., exclusive of the D9S59 and D9S127 polymorphisms) in terms of their nucleotide identity or location and do not define the gene associated with familial dysautonomia in terms of a particular chemical structure.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant application, the specification teaches the polymorphisms D9S53, D9S58, D9S105, D9S309, D9S310, D9S172 and D9S174 which are located within the region between D9S59 and D9S127 (see page 38 and Table 1). The specification (page 28) teaches that the region from D9S59 to D9S127 spans about 19 cM of DNA (i.e., approximately 19 million base pairs). Given the extensive size of this region, a significant number of polymorphisms would be expected to occur within this 19 million base pair region. Accordingly, the disclosure of 7 polymorphisms is not considered to be representative of the broadly claimed genus.

Further, the claims require that the polymorphism is linked to a gene associated with FD, such that detection of the polymorphism is indicative of an individual that is a carrier of a gene associated with FD. However, the specification does not disclose any particular genes that are associated with FD. Rather, the specification teaches only a chromosomal fragment from the region of chromosome 9q31-9q33, and particular polymorphic markers within this region that are genetically linked to the occurrence of FD (see Tables 2 and 3). There are no teachings in the specification or in the prior art as to the length of the gene, the number of introns and exons present in the gene, the positions of the exons and introns in the gene, the precise location of the gene, the nucleotide sequence of any portion of the gene, the sites of initiation or termination of

the gene or the functional activity of any protein encoded by the gene. Also, the specification (page 3) refers to "the gene causing familial dysautonomia" and to the "defective gene." However, since all individuals would be considered to be carriers of the FD gene since the gene is present in all individuals, only the mutated gene would be considered to be associated with causing familial dysautonomia. Thereby, the claims appear to also be inclusive of polymorphisms that are linked to a gene that is causative of familial dysautonomia. However, the specification has also not disclosed any genes that cause FD , such a mutated form of a wildtype FD gene. Accordingly, no wildtype FD genes or defective genes causing FD have been disclosed in terms of their complete structure.

It is then determined whether a representative number of species within the claimed genus have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for additional polymorphisms or for a wildtype or defective gene associated with familial dysautonomia.

While at the time of filing applicants were in possession of the polymorphisms D9S59, D9S127, D9S53, D9S58, D9S105, D9S309, D9S310, D9S172 and D9S174 wherein the polymorphisms are linked to FD and thereby were in possession of methods for detecting said polymorphisms, the limited information provided in the specification is not deemed sufficient to reasonably convey to one of skill in the art, that at the time of filing, Applicants were in possession of the broadly claimed genus of any

polymorphism in the region between D9S59 and D9S127, and particularly any polymorphism linked to a wildtype or defective gene associated with familial dysautonomia. Thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to remarks:

In the response, Applicants state that the nature of the gene responsible for FD is not necessary in order to perform linkage analysis to identify polymorphisms. It is asserted that the specification teaches that linkage analysis can be performed to determine the location of a gene causing a hereditary disorder and does not require any knowledge of the biochemical nature of a disease. It is also stated that the specification teaches that the location of a gene can be used for prenatal diagnosis before the altered gene that causes the disease is found. Thereby, Applicants conclude that only the chromosomal location is required to identify a polymorphism.

This argument has been fully considered but is not persuasive. The present claims require the detection of a polymorphism "linked to a gene associated with familial dysautonomia" wherein "the polymorphism is indicative of carriers of a gene associated with familial dysautonomia." Thereby, to perform the claimed method requires knowledge of the structure/identity of the gene associated with FD. However, as discussed in the above rejection, the specification does not disclose any particular

genes that are associated with FD. Rather, the specification teaches only a chromosomal fragment from the region of chromosome 9q31-9q33, and particular polymorphic markers within this region that are genetically linked to the occurrence of FD (see Tables 2 and 3). There are no teachings in the specification or in the prior art as to the length of the gene, the number of introns and exons present in the gene, the positions of the exons and introns in the gene, the precise location of the gene (on chromosome 9 or on another chromosome), the nucleotide sequence of any portion of the gene, the sites of initiation or termination of the gene or the functional activity of any protein encoded by the gene.

The naming of a gene by its function is not sufficient to describe that gene. In Amgen v. Chuzai, the Court of Appeals for the Federal Circuit stated that "it is not sufficient to define (a DNA) solely by its principal biological property, e.g. encoding of human erythropoietin." Id. at 1021. Rather, what is necessary is that (the applicant) provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id. at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 35 USC 112 first paragraph written description requirement. More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lillv and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a cDNA by its function 'tis only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description does not define any structural features commonly

possessed by members of the genus that distinguish them from others." In the present situation, the description of a gene in terms of its association with FD is not sufficient to describe the structure of that gene and allow for one to distinguish that gene from any other gene.

The response asserts that a gene associated with FD refers to a gene that is defective or mutated. It is stated that only the defective gene will be associated with FD and not the wildtype gene. Applicants also point to parent application 08/480,655 (U.S. Patent 5,998,133) as reciting the language "gene associated with familial dysautonomia." These arguments have been fully considered but are not persuasive. It is first noted that the present application has been examined on its own merits herein. Further, as discussed in the above rejection, the specification (page 3) refers only to "the gene causing familial dysautonomia" and to the "defective gene." The specification does not provide a definition for the phrase "gene associated with familial dysautonomia" and specifically does not define this phrase as referring only to a "defective" gene and not to a wildtype gene. Thereby, it is maintained that the claims encompass the detection of both polymorphisms linked to a wildtype FD gene and a mutant FD gene. Importantly, it is emphasized that in addition to the fact that the specification has not disclosed a particular wildtype FD gene, the specification has not disclosed any FD genes that include a mutation that is causative or otherwise correlated with the occurrence of familial dysautonomia.

The response appears to suggest that the specification discloses the location of the gene. However, a particular chromosomal location for a gene associated with FD

has not been disclosed in the specification. Further, it is noted that the claims are not limited to genes at any particular location on chromosome 9 or any other chromosome. Rather, the claims require only that the polymorphism is located between D9S59 and D9S127. The gene associated with FD is not defined in terms of any specific structural attributes, including the location of the gene.

It is also noted that claims 26-28 specifically require correlating the presence or absence of a polymorphism with the presence or absence of a gene associated with FD. The claims also require determining segregation between the polymorphism and "the familial dysautonomia gene." This fact further illustrates the criticality of the gene to the claimed methods since one cannot determine whether a gene is present or absent or whether a polymorphism segregates with a gene without knowledge of the identity of that gene.

The response asserts that the specification has taught a representative number of polymorphisms linked to a gene associated with FD. It is stated that any polymorphisms in the range of D9S59 to D9S127 will have similar or better LOD scores than the flanking markers and thereby will be positively linked to the gene as well. It is argued that the description provides evidence that Applicant was in possession of the common attributes of the members of the genus. These arguments have also been fully considered but are not persuasive. While Applicant's teach the locations of the polymorphisms of D9S59 and D9S127, the polymorphisms within the claimed genus of any polymorphism in the region between D9S59 and D9S127 do not share common

structural attributes. Rather, each polymorphism is expected to consist of a unique nucleotide sequence and is located at a distinct nucleotide position on chromosome 9. Further, "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895." Thereby, a showing of how to potentially identify and make polymorphisms is not sufficient to establish that Applicant's were in possession of the invention of any polymorphism located between D9S59 and D9S127 and linked to a gene associated with FD.

Claim Rejections - 35 USC § 112 - Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-28 and 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting the presence of a polymorphism wherein the polymorphism is selected from the group consisting of D9S59, D9S127, D9S53, D9S58, D9S105, D9S309, D9S310, D9S172 and D9S174 , does not reasonably provide enablement for methods for detecting the presence of any polymorphism located between D9S59 to D9S127 wherein the polymorphism is linked to a gene associated with FD and wherein the presence of the polymorphism is indicative of carriers of a gene associated with FD. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to a method for detecting the presence of a polymorphism linked to a gene associated with familial dysautonomia (FD) comprising analyzing a region of chromosome 9 for a polymorphism located between D9S59 and D9S127 inclusive wherein the presence of the polymorphism is indicative of carriers of a gene associated with familial dysautonomia. The claims do not define the structure of the polymorphisms located between D9S59 to D9S127 in terms of their nucleic acid sequence, location or length and do not define the gene associated with familial dysautonomia in terms of a particular nucleic acid sequence. The region from D9S59 to D9S127 spans over 19 cM of DNA or approximately 19 million base pairs (see page 28). Given the extensive size of this region, the claims encompass detecting a significantly large number of polymorphisms that have not been defined in terms of their nucleotide identity or specific location within chromosome 9. Further, the claims require that the polymorphism is linked to a gene associated with FD, such that detection of the polymorphism is indicative of an individual that is a carrier of a gene associated with FD. However, the gene is not defined in terms of any particular structural features such as

the nucleotide sequence of the gene, the length of the gene, the number of introns and exons present in the gene, the positions of the exons and introns in the gene, the precise location of the gene, the sites of initiation or termination of the gene or the functional activity of any protein encoded by the gene. Also, the claims appear to encompass the detection of polymorphisms linked to a defective/mutated gene that is causative of FD and the detection of polymorphisms that are within the FD gene itself and which are causative of FD.

Additionally, claims 26-28 further require correlating the presence of a polymorphism with the presence or absence of the gene associated with FD.

Nature of the Invention

The claims encompass methods of detecting a polymorphism linked to a gene associated with FD. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the polymorphisms D9S59, D9S127, D9S53, D9S58, D9S105, D9S309, D9S310, D9S172 and D9S174, which are located within the region between D9S59 and D9S127 (see page 38 and Table 1). The specification also teaches a linkage analysis between these polymorphisms and FD (see, e.g., page 33). Genotyping was performed for 353 different FD chromosomes from 26 linkage families and 148 families with single affected individuals. In particular, the markers D9S127,

D9S58 and D9S59 were found to have significant LOD scores, establishing their association with FD (see Figure 2).

The specification (page 3-4) states that linkage analysis can be used to find the location of a gene causing FD. However, the present specification does not actually identify the specific location of the FD gene. Rather, the specification teaches a region of chromosome 9 that is linked to the occurrence of FD.

The specification (page 6) also states that the inheritance of genetic markers within a family can be used to identify individuals that are carriers of a marker indicative of FD because affected individuals will carry the same form of the marker while all unaffected individuals will carry at least one different form of the marker. However, the present claims are not directed to methods for diagnosing risk of developing FD by performing inheritance studies wherein the transmission of a marker from affected family members is detected. Rather, the claims require the detection of any polymorphism between D9S59 to D9S57 as indicative of a carrier of a gene associated with FD.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying polymorphisms that are linked to a gene associated with a disorder is highly unpredictable in the absence of knowledge of the gene itself. It appears that the claims seek to encompass methods which detect the presence of carriers of a gene that is causative of FD. However, the specification does not teach any gene associated with FD and does not teach any defects in a gene that would be

causative of FD. The teachings in the specification of polymorphisms present within 9q31 and the teachings that particular polymorphisms in this region are linked to the FD disease is not equivalent to teaching specific wildtype or defective genes that are linked to FD. Knowledge of the presence of a polymorphism linked to FD does not allow one to predict the structure of a gene associated with FD.

Once a region of the genome is identified as being associated with a disease extensive experimentation remains to determine which, if any, genes within this region are sufficiently linked to a disease. Further, once a gene associated with a disease is identified, significant experimentation is required to identify particular mutations and polymorphisms within the gene that are diagnostic of the disease. In the present situation, the ability to isolate the FD gene is particularly unpredictable because no information concerning the functional or structural characteristics of the gene are disclosed in the specification or in the prior art. For example, there are no teachings in the specification or in the prior art as to the length of the gene, the number of introns and exons present in the gene, the precise location of the gene, the nucleotide sequence of any portion of the gene, the sites of initiation or termination of the gene or the functional activity of any protein encoded by the gene.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to identify a specific FD gene that is within the region of D9S59 to D9S127. The specification (page 29) states that "(t)the next step of cloning the gene will involve exon trapping, screening

of cDNA libraries, Northern blots or RT-PCR of autopsy tissues from affected and unaffected individuals, direct sequencing of exons or testing of exons by SSCP (single strand conformation polymorphism), RNase protection or chemical cleavage, or any other state-of-the art technique." While each of these methods was known in the art at the time the invention was made, the outcome of performing such methods is highly unpredictable. The novelty of the claimed invention is not based on general methods for analyzing a region of chromosome 9 by performing exon trapping, Northern blotting etc. Rather, the novelty of the invention is based on the identity of the particular polymorphisms that are to be detected. Since the polymorphisms are defined as being linked to the FD gene, and their presence is characterized as indicative of a carrier of a gene associated with FD, to practice the claimed invention requires knowledge of a gene associated with the occurrence of FD. However, the specification does not provide sufficient guidance as to how to identify such a gene.

Regarding claims 26-28, the claims require correlating the presence of the polymorphism with the presence or absence of the gene associated with FD. However, again, the specification does not teach or provide sufficient guidance as to how to obtain the gene associated with FD. Additionally, claim 28 requires correlating the presence of a polymorphism with a corresponding polymorphism pattern for family members showing segregation between a polymorphism and the FD gene. However, the specification does not teach any particular polymorphism patterns that are associated with FD. The specification also does not teach how to correlate a polymorphism with a

polymorphism pattern. It is unpredictable as to what would be the identity of a specific polymorphism pattern that would be associated with FD.

Further, regarding claim 29, the claim requires linking the distribution of maternal and paternal polymorphisms with FD. However, the specification does not provide sufficient guidance as to how to perform a general step of determining the distribution of a maternal and paternal polymorphism and linking the occurrence of the polymorphism to FD.

Working Examples:

The specification provides working examples of methods for detecting the polymorphisms D9S59, D9S127, D9S53, D9S58, D9S105, D9S309, D9S310, D9S172 and D9S174. However, because the claims do not define the structure of the polymorphism to be detected, the claims encompass the detection of any polymorphism of any identity within a 19 million base pair region of chromosome 9q31. The claims appear to be inclusive of polymorphisms that are within the FD gene itself and which are causative of FD. However, the specification does not exemplify any polymorphisms within an FD gene or any polymorphisms causative of FD. The specification also does not exemplify any particular genes that are associated with FD or any polymorphisms that are indicative of a carrier of a defective gene associated with FD.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach any wildtype or defective / mutated genes associated with FD and does not teach a representative number of polymorphisms within the region of D9S59-D9S127 that are linked to a gene associated with FD and indicative of carriers of a gene associated with FD. Although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to remarks:

In the response, Applicants traversed this rejection by stating that the structural features of the gene are not required to perform Applicants' invention. It is stated that

based on linkage analysis one can identify polymorphisms that segregate with the FD phenotype. It is also stated that the present claims are not directed to a method for identifying an FD gene.

Applicants' arguments have been fully considered but are not persuasive. While the present claims are not directed to a method for identifying a gene, the present claims do require identifying a polymorphism linked to a gene associated with FD. However, the specification and claims do not provide any structural attributes to describe the FD gene. It is maintained that the identity of the gene is in fact essential to the claimed method since one can only ascertain whether a polymorphism is linked to a gene associated with FD if one has knowledge of what constitutes a gene associated with FD.

Further, claims 26-28 specifically require correlating the presence or absence of a polymorphism with the presence or absence of a gene associated with FD. The claims also require identifying family members showing segregation between "the familial dysautonomia gene and the polymorphism." To determine whether a gene is present or absent requires knowledge of what constitutes that gene. Similarly, determining whether a polymorphism segregates with "the" FD gene, requires knowledge of the identity of the FD gene. Thereby, it is maintained that the identity of the gene associated with FD is in fact essential to the claimed invention.

The response states a "gene associated with FD" refers to a gene that is defective or mutated. It is stated that only the defective gene will be associated with FD and not the wildtype gene. These arguments have also been fully considered but are

not persuasive. As discussed in the above rejection, the specification (page 3) refers only to "the gene causing familial dysautonomia" and to the "defective gene." The specification does not provide a definition for the phrase "gene associated with familial dysautonomia" and specifically does not define this phrase as referring only to a "defective" gene and not to a wildtype gene. Thereby, it is maintained that the claims encompass the detection of both polymorphisms linked to a wildtype FD gene and a mutant FD gene. Moreover, it is again emphasized that in addition to the fact that the specification has not disclosed a particular wildtype FD gene, the specification has not disclosed any FD genes that include a mutation that is causative or otherwise correlated with the occurrence of familial dysautonomia.

The response states that nine working examples have been provided showing polymorphisms that segregate with the FD phenotype. While it is agreed that nine polymorphisms within the region of D9S59 to D9S127 have been described (i.e., D9S59, D9S127, D9S53, D9S58, D9S105, D9S310, D9S172 and D9S174), the specification has not established that these polymorphisms are linked to a particular gene associated with FD. Rather, as stated by Applicants, the specification establishes that these 9 polymorphisms segregate with the inheritance of the FD phenotype.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-28 and 30-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,998,133. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '133 are both inclusive of methods for detecting the presence of a polymorphism wherein the polymorphism is between the markers D9S53 and D9S105. It is noted that the makers D9S53 and D9S105 are located within the region of D9S59 to D9S127 and the D9S105 marker is within the region of D9S58 to D9S59, as recited in the present claims.

Response to remarks:

In the response, Applicants requested that the rejection be held in abeyance pending the determination of patentable subject matter. However, the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained and made final for the reasons stated above.

7. Claims 20-28 and 30-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No.

5,387,506. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '506 are both inclusive of methods for detecting the presence of a polymorphism wherein the polymorphism is between the markers HXB and D9S109. It is noted that the makers HXB and D9S109 are located within the region of D9S58 to D9S59 and D9S59 to D9S127, as recited in the present claims.

Response to remarks:

In the response, Applicants requested that the rejection be held in abeyance pending the determination of patentable subject matter. However, the Office does not hold rejections in abeyance. Accordingly, the rejection is maintained and made final for the reasons stated above.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 20-25 and 33 rejected under 35 U.S.C. 102(a) as being anticipated by Kwiatkowski (Genomics. Feb 1992. 12: 220-240; cited in the IDS).

Kwiatkowski (pages 230 and Table 2) teaches a method comprising analyzing human chromosome 9 of a subject and detecting the presence of a D9S59 polymorphism. The D9S59 polymorphism is located "between D9S59 and D9S127 inclusive." Since the present claims specifically include the detection of the D9S59

polymorphism, it is considered to be an inherent property of the D9S59 polymorphism that this polymorphism is linked to a gene that is associated with familial dysautonomia and that detection of the polymorphism necessarily identifies carriers of a gene associated with familial dysautonomia.

Regarding claims 21-25, it is a property of the D9S59 polymorphism that this polymorphism is located on the q31 band of the long arm of chromosome 9 and is located about 10 to 20cM around the D9S309 and D9S310 markers.

Response to remarks:

In the response, Applicants traverse this rejection by stating that Kwiatkowski describes a nucleic acid sequence for detecting the polymorphism D9S59 but does not teach that this polymorphism is linked to the FD gene or is a marker to identify individual's carrying the gene associated with FD. This argument has been fully considered but is not persuasive. The present claims are drawn to a method for detecting a polymorphism located between D9S59 and D9S127 inclusive. Kwiatkowski teaches a method for detecting the D9S59 polymorphism and thus the method of Kwiatkowski includes each of the same method steps as that of the claimed invention. There is no requirement for Kwiatkowski to teach that the D9S59 polymorphism is linked to a gene associated with FD because It is considered to be an inherent property of the D9S59 polymorphism that this polymorphism is linked to a gene associated with FD. Applicants have not provided any arguments or evidence to contradict the finding that D9S59 is linked to a gene associated with FD.

The response further asserts that U.S. Patents 5,998,133 and 5,387,506 were both originally rejected as anticipated by Kwiatkowski, but were found to be subsequently allowable over the prior art. The response also asserts that the claims of these patents have substantially the same language as the instant claims. However, regardless of the similarity in claim language, the present grounds of rejection are maintained. As stated above, Applicants' traversal on the grounds that Kwiatkowski does not teach that the D9S59 polymorphism is linked to a gene associated with FD were not found to be persuasive. No additional arguments directed to the current grounds of rejection have been provided by Applicants. Further, it is noted that the previous and current Office actions have been signed by a Tech Center Director.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634

Director TC 1600 (acting)

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER